Remarks

Claims 16 and 17 are pending in the subject application. New claim 18 is provided above for which support is found throughout the present application. Accordingly, claims 16-18 are now before the Examiner for review.

Claims 16 and 17 were rejected under 35 USC § 112, first paragraph, as pertaining to new subject matter. Applicants respectfully traverse. Applicants respectfully assert that the Examiner is taking an overly restrictive interpretation of the passages cited to support these claims. For convenience, Applicants provide the language of paragraph 0023 of the present application, which Applicants believe is most pertinent:

> This invention relates to a method of treating hypertension comprising administering a therapeutically effective amount of an agent capable of reducing uric acid levels in a patient in need of such treatment. A reduction in uric acid levels would reduce the risk of hypertension, coronary heart disease, renal dysfunction, cardiovascular morbidity and mortality. Current standards for elevated uric acid levels are 7 mg/dl. However, patients with uric acid levels of 10 mg/dl are a high risk for the above-noted cardiovascular conditions, between 6 and 10 mg/dl are at an increased risk for the above-noted cardiovascular conditions, or a reduced risk with uric acid levels of >4 and <6 mg/dl. (Emphasis added)

Applicants assert that a fair and straightforward interpretation of this paragraph supports claims 16 and 17. The paragraph teaches that hypertension is treated by reducing uric acid levels. The paragraph then teaches that uric levels of between 4-6 mg/dl are targeted, since this range pertains to a reduced risk of the noted cardiovascular conditions, namely hypertension. Claim 16 and 17 are directed to a method of treating hypertension by reducing uric acid levels to a range of 4-6 mg/dl. Applicants assert that anyone skilled in the art would appreciate that this is the plain-meaning of what is set forth in paragraph 0023. M.P.E.P 2163.07 explains that "Mere rephrasing of a passage does not constitute new matter. Accordingly, a rewording of a passage where the same meaning remains intact is permissible. *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973)." Any differences between the exact language in paragraph 0023 and

claims 16 and 17 unquestionably relate only to a mere rephrasing, which is clearly permitted under long-standing patent law principles. In view of the foregoing clarifying remarks, Applicants respectfully request reconsideration of this 35 USC § 112, first paragraph, rejection.

Claims 16-17 are rejected under 35 USC § 112, second paragraph, as being indefinite. The basis of this rejection appears to be that one skilled in the art could not ascertain the metes and bounds as to therapeutically effective amount of xanthine oxidase inhibitor to achieve a uric acid level in the patient of 4 to 6 mg/dl. Applicants respectfully traverse. Applicants respectfully assert that one skilled in the art would understand this claim language to pertain to administering to a patient an amount of a xanthine oxidase inhibitor that will achieve a level of 4-6 mg/dl in the plasma of the patient. Indeed, the Examiner appears to fully apprehend what this limitation means based on the rationale presented in the office action alleged in support of the obviousness rejections of claims 16 and 17 found later in the office action. In particular, the office action at page 5 states that it would have been obvious to one skilled in the art to determine effective amounts of xanthine oxidase inhibitor needed to achieve uric acid levels in the patient of 4 to 6 mg/dl. For reasons that are discussed below, Applicants vigorously disagree with the obviousness of claims 16 and 17. However, it is hard to understand how the Examiner views a limitation of claims 16 and 17 as being indefinite and obvious simultaneously. To further address the alleged indefiniteness issue, Applicant will be providing objective evidence by way of an Expert Declaration to establish that one skilled in the art would readily comprehend all of the claim language of claims 16 and 17. Applicants respectfully request reconsideration of this 35 USC § 112, second paragraph, rejection.

Claims 16-17 were rejected under 35 USC § 103(a) as being obvious over Maeda et al. (U.S. Patent No. 5,747,495) in view of Ward. Applicants respectfully traverse. The office action states that Maeda et al. do not teach administration of a therapeutically effective amount of a xanthine oxidase inhibitor to achieve a uric acid level in the patient of 4 to 6 mg/dl. Applicants agree with this assessment. However, the office action then cites to Ward for the proposition that uric acid is a risk factor, and therefore it would have been obvious to test dosages to reach an optimal range of uric acid. Applicants disagree.

A careful read of the Ward paper reveals that in actuality, Ward makes no real comment about uric acid being causal, but rather only concludes that it may be an early indicator. Ward states that "For now, it seems safe to conclude that hyperuriceaemia in hypertension may be an early indicator of hypertensive cardiorenal disease, which is commonly associated with multimetabolic syndrome." Moreover, Ward goes in the opposite direction by even explaining how uric acid may play a protective role for hypertension. "An antioxidant role for uric acid also seems plausible since blood concentrations of purines such as adenosine hypoxanthine and uric acid usually rise after coronary occlusion in clinical studies. Bottom line: Ward does not teach that uric acid causes hypertension and therefore it is too far of a stretch to say that the skilled artisan would have been led to work out dosages to achieve the ranges of uric acid specified in claims 16 and 17.

Furthermore, Ward must be considered in view of other papers in more pertinent journals emphatically asserting that uric acid is irrelevant to cardiovascular diseases, such as hypertension, so much so that uric acid should not even be tested. In 1999, Cullenton et al. published the famous Framingham Heart Study (Attachment A). Cullenton et al., though recognizing that there has been a long association between elevated uric acid levels and cardiovascular disease assert the following:

> "[O]ur findings from a community-based prospective study of 6763 adult men and women suggest that an elevated serum uric acid level is not causally associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes. …From a clinical perspective, serum uric acid level should not be used as an indicator of risk for cardiovascular disease; established risk factors should be used to stratify risk." (emphasis added).

Also, in 1999, Vaccarino and Krumholz, practically shut the book on uric acid having any role in cardiovascular disease (Risk Factors for Cardiovascular Disease: One Down, Many More to Evaluate, see Attachment B):

> "many epidemiologic studies have sought to clarify the role of this risk factor [uric acid levels]. In addition, laboratory studies have attempted to identify the mechanism by which an elevated uric acid level causes an increased risk for cardiovascular disease. Despite these efforts the role of uric acid as a risk factor was never fully resolved."

Commenting on the Framingham Heart Steady, Vaccarino and Krumholz state that Cullenton et al. "resolve the long-standing controversy surrounding the role of uric acid as a risk factor for cardiovascular disease. … They found no association between uric acid levels and any of the outcomes in men or women."

Thus, at the time of filing the present application, experts in the field did not believe that uric acid caused hypertension rather it was believed uric acid was merely correlative with, or a consequence of hypertension. That is, it was believed that high blood pressure impaired kidney function and therefore impaired excretion of uric acid. The wisdom of the day was that elevated uric acid levels might be an indicator that one is at risk of high blood pressure, but not that uric is the cause.

In the context of the present situation, Ward, or any others who thought that uric acid may be an associative risk factor for hypertension, does not, by any reasonable standard, translate into Ward teaching that uric acid causes hypertension. Certainly, it cannot be reasonably said that Ward taught the skilled artisan dosages of xanthine oxidase inhibitors are to be determined so that a specific level of uric acid is achieved to in turn produce an effect on hypertension.

While the Applicants acknowledge that uric acid was known as a possible risk factor for hypertension (incidentally, this point is not yet even fully settled in the art), Applicants' fundamental discovery is that uric acid is a causal factor for hypertension. This discovery was based on data showing that raising uric acid in an oxonic acid rat model (as opposed to the flawed spontaneous hypertension model) led to hypertension. The Applicants discovered that administering rats an uricase inhibitor led to a rise in blood pressure after several weeks and that lowering the uric acid with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone) could either prevent the development of hypertension or treat the hypertension. Furthermore, it was this

discovery that revealed that hypertension could be controlled by controlling uric acid levels. The inventors' discovery has since been confirmed in human experiments wherein a decrease in blood pressure is directly associated with an intentional reduction of uric acid levels in patients. (See paragraphs 10 and 11 of previously submitted Johnson Declaration).

To summarize, the intentional reduction of uric acid in humans is not taught or suggested by the Maeda et al. paper and/or the Ward paper. Furthermore, Maeda et al.'s study in the flawed SHR rat model which fails to contemplate the effects of uric acid does not render obvious the intentional reduction of uric acid in humans, much less the reduction of uric acid below a specified level. This is not cured by the Ward paper, which suggests hat uric acid might be an associative risk factor, but falls short of suggesting that uric acid is causative. The inventors somewhat serendipitous studies utilizing their newly developed model system ultimately led to the discovery that uric acid was not only a risk factor, it is a causal factor. Based on this discovery by the inventors, they could then surmise that controlling uric acid levels would treat hypertension. Accordingly, the Maeda et al. paper, either alone, or in conjunction with the Ward paper does not destroy the inventiveness of claims 16 and 17.

Furthermore, with respect to utilizing the distinct xanthine oxidase inhibitor allopurinol as claimed in claims 17 and 18, a recent article by Mellen et al. published in the scientific journal *Hypertension* (April, 2007) bolsters the nonobviousness of utilizing the inhibitor allopurinol as an agent to treat hypertension. See attachment A. This article cites to Dr. Johnson's work and states that "the failure of allopurinol to prevent hypertension in spontaneously hypertensive rats does not necessarily contradict the hypothesis that uric acid plays a causal role in human hypertension. What is clear from this article is that studies utilizing the SHR rat model have failed to show that allopurinol can treat hypertension. Thus, notwithstanding an observation of an unsustainable, transient effect of allopurinol on blood pressure in the SHR rate noted in the previously cited Miyamoto paper, studies by Trachtman (Hypertension 1991; 17:194-202), Laakso (Hypertension 1998; 32:902-906) and Maenishi (Hypertension 1997; 19:461-467) all failed to show significant effects of allopurinol on lowering BP. As Dr. Johnson elaborately explained in his previously submitted declaration, this is due to the unique

etiology of hypertension in the SHR model, and those studying the SHR model would not have been able to discover that allopurinol is a causative factor. Indeed, the negative longterm studies with allopurinol to lower BP in the SHR rat likely steered away most investigators from considering allopurinol a means to treat hypertension. See paragraphs 2-7, Johnson Declaration. Accordingly, separate from the comments concerning any xanthine oxidase inhibitor, the inventiveness of utilizing the distinct xanthine oxidase inhibitor allopurinol must be acknowledged over the cited Maeda et al. and/or Ward papers. Based on the foregoing remarks, Applicants respectfully request the reconsideration and withdrawal of this 35 USC § 103(a) rejection.

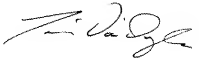
Next, claim 16 is rejected under 35 USC § 103(a) as being obvious over Baldwin et al. in view of Ward. Applicants respectfully traverse. With respect to the Baldwin reference Applicants reiterate their remarks provided in their supplemental amendment dated November 21, 2006. The Office Action acknowledges that Baldwin does not teach administration of a xanthine oxidase inhibitor to achieve a uric acid level according to that specified in claim 16. The Examiner cites to the Ward paper for purpose of trying to cure this deficiency. Applicants again respectfully point out that Ward does not teach that uric acid is a causal factor. The combination of Baldwin with Ward does not reasonably suggest that the levels of uric acid in claim 16 should be attained to treat or prevent hypertension. Applicants respectfully ask that the Examiner consider the wealth of papers at the time of filing (and even well after that time) arguing that elevated uric acid levels are not causal and may even be beneficial. Applicants assert that considering the failure of studies using xanthine oxidase inhibitors in the SHR rate model have ultimately failed (as acknowledged by Mellen et al.), it cannot be legitimately said that it would have been obvious to target controlling uric acid levels as a treatment for hypertension. Based on the attachments and foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103(a) rejection.

Claims 16 and 17 are rejected under 35 USC § 103(a) as being obvious over Nakamoto in view of Ward. Applicants respectfully traverse. First, Applicants do acknowledge that Nakomoto does not teach or suggest achieving levels of 4 to 6 mg/dl to treat hypertension. However, Applicants note that the one line cryptic comment in Nakomoto concerning that the specific compound treats gout and may have a curative

effect on hypertension baldly stands alone without any scientific rationale, supporting data, or even a cross-reference. Nakamoto does not even teach the mechanism by which dimethylheptylphenyl butanoyl ethanolamine compound works. It does not appear to even be a xanthine oxidase inhibitor. For fairness sake, it cannot be reasonably said that this one confusing statement concerning an unknown compound can suggest the use of a xanthine oxidase inhibitor to treat hypertension. For the reasons set forth above for Maeda and Baldwin, the Ward paper does not cure the deficiencies of the primary Nakamoto reference. Applicants respectfully request reconsideration and withdrawal of this 35 USC § 103(a) rejection.

Applicant asserts that all grounds for rejection of the pending claims are addressed and obviated. It is respectfully urged that this application is in condition for allowance. Applicants request that the Examiner call the undersigned if clarification is needed on any aspect of this Reply, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application.

Respectfully submitted,



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